microtubule nucleators are distributed inhomogeneously. Two mechanisms, which are not mutually exclusive, have been proposed to date: a gradient of nucleators around chromatin (Caudron et al., 2005) and a microtubule-mediated nucleation process (Clausen and Ribbeck, 2007). In the future, the approach presented in this study—that is, combining innovative experimental techniques with mathematical modeling and simulations (Loughlin et al., 2010)—may prove to be helpful to investigate this question.

ACKNOWLEDGMENTS

M.D. is supported by a NWO-ALW VICI grant and by the Stichting voor Fundamenteel Onderzoek der Materie (FOM), which is financially supported by the Nederlandse organisatie voor Wetenschappelijk Onderzoek (NWO).

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Dialing Down SUN1 for Laminopathies

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DOI 10.1016/j.cell.2012.04.003

Laminopathies, caused by mutations in A-type nuclear lamins, encompass a range of diseases, including forms of progeria and muscular dystrophy. In this issue, Chen et al. provide evidence that elevated expression of the nuclear inner membrane protein SUN1 drives pathology in multiple laminopathies.

Since their initial link to human disease, A-type nuclear lamins have been the subject of intense scrutiny. Mutations, mostly missense ones, in *LMNA*, the gene that encodes all A-type lamins by alternative splicing (lamins A and C are the most prominent), cause diseases ranging from dystrophic syndromes (including forms of muscular dystrophy, lipodystrophy, and dilated cardiomyopathy) to progeroid disorders such as Hutchinson-Gilford progeria syndrome (HGPS), which present with a rapid onset of a subset of pathologies that are associated with normal aging (Burtner and Kennedy, 2010). Why do different mutations in a structural component of the nucleus cause such an array of debilitating disorders?

Mouse models of a wide spectrum of laminopathies have been developed, ranging from a knockout of the *LMNA* gene, which dies at 6–8 weeks of age with dilated cardiomyopathy and skeletal muscle dystrophy (Sullivan et al., 1999), to mice engineered to express human disease mutations (Cohen and Stewart, 2008). The models generally recapitulate their respective human disease phenotypes and serve to uncover mechanisms underlying pathophysiology and disease progression. As a starting point for the study by Chen et al. (2012), a double-knockout mouse was created lacking both A-type lamins and SUN1. SUN1 interacts with lamin A/C as components of the linker of nucleoskeleton and cytoskeleton (LINC) complex, which mediates crosstalk between the actin cytoskeleton and the nucleus, leading to large-scale nuclear movements within the cell (Meinke et al., 2011). The expectation was that loss of SUN1 would exacerbate the already severe skeletal muscle and cardiac phenotypes in the *Lmna* knockout, but to the authors' surprise, the reverse was true. The $Lmna^{-/-}$ $Sun1^{-/-}$ mice survive significantly longer than $Lmna^{-/-}$ single knockouts, resisting a range of $Lmna^{-/-}$ pathologies, including lordokyphosis, growth defects, reduced bone density, and cardiac/skeletal muscle defects (Figure 1; Chen et al., 2012).

There was already reason to believe that the LINC complex might be linked to laminopathies, as mutations in another LINC component, Emerin, cause Emery-Dreifuss muscular dystrophy. Loss of A-type lamins leads to mislocalization of other LINC components (Vaughan et al., 2001, Muchir et al., 2003), but prior to this study, it was not known how SUN1 would be affected. In embryonic fibroblasts from $Lmna^{-/-}$ mice, Chen et al. make two important observations—first that SUN1 is highly overexpressed and second that a substantial portion of the

protein is enriched in the Golgi after localization to the nuclear periphery is presumably saturated (Chen et al., 2012). RNAi-mediated knockdown of SUN1 rescued nuclear morphology and proliferation defects. Thus, reduced SUN1 expression rescues cellular as well as organismal defects associated with loss of A-type lamins. Inhibition of SUN1 Golgi localization also provided partial rescue, suggesting that hypermorphic or neomorphic functions of SUN1 in the Golgi might drive pathology in the *Lmna*$^{-/-}$ context.

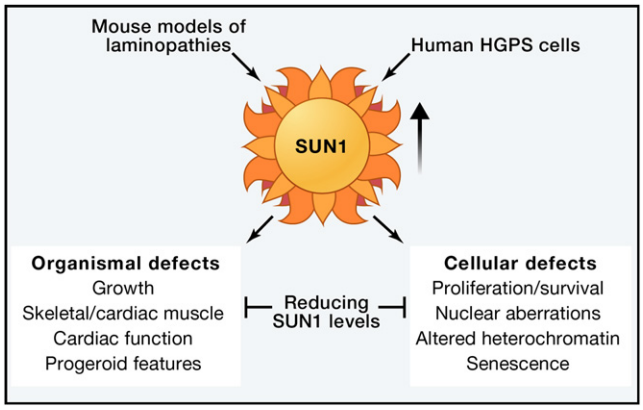

Figure 1. Accumulation of Sun1 Is Pathogenic in Laminopathies
In dystrophic *Lmna*$^{-/-}$ and progeric *Lmna*Δ9 mouse models, inner nuclear envelope protein SUN1 accumulates. Removal of *Sun1* in *Lmna*$^{-/-}$ or *Lmna*Δ9 mice leads to reduced tissue pathologies and enhanced longevity. Likewise, in human Hutchinson-Gilford progeria syndrome cells, SUN1 amasses, and reducing its levels corrects nuclear and cellular defects. Hence, SUN1 may be a prime target for interventions and therapies.

To investigate this surprising finding further, Chen et al. turned to another *LMNA* mutant mouse with progeroid phenotypes and an interesting history. The most common *LMNA* mutation giving rise to HGPS is G608G, a silent mutation that activates a cryptic splice site creating an in-frame lamin A protein lacking 50 amino acids in the C terminus, termed progerin (Burtner and Kennedy, 2010). Mice had been engineered to express an Emery-Dreifuss human disease variant, *LMNA-L530P*, with the expectation of generating a better muscular dystrophy model (Mounkes et al., 2003). Unexpectedly, a splicing defect in *LMNA* was apparent in the *L530P* allele, removing 40 amino acids and rendering this mutant allele similar but nonidentical to the progerin allele. These mice are referred to as *Lmna*Δ*9* mutants, and Chen et al. found that *Lmna*$^{\Delta 9/\Delta 9}$ *Sun1*$^{-/-}$ double-mutant mice live longer than their *Lmna*$^{\Delta 9/\Delta 9}$ counterparts, with associated rescue of cellular and organismal phenotypes (Chen et al., 2012). That reduced expression of SUN1 rescues both *Lmna*$^{-/-}$ and *Lmna*$^{\Delta 9/\Delta 9}$ is surprising because they are thought to model different diseases.

Finally, Chen et al. investigated the role of SUN1 in HGPS human fibroblasts. Again, SUN1 is overexpressed in these cells, consistent with an earlier report (Haque et al., 2010). Reduction of SUN1 by RNAi improved nuclear morphology and, in this case, rescued defects in heterochromatin profiles and premature senescence (Chen et al., 2012). However, there was no excess SUN1 in the Golgi detected; instead, increased SUN1 protein appeared to remain nuclear. The reasons for this are unclear. It will be important to resolve these differences in future studies, as some of the potential explanations run counter to the notion of pathology being driven by toxicity in the Golgi. One model put forward by the authors is that HGPS human cells are more sensitive to Golgi SUN1 and adapt in culture to keep levels at a minimum. Specific consequences resulting from expression of progerin per se may also be involved in the differences between the mouse models and human patient cells.

What do we make of these findings? The take-home message is that SUN1 is overexpressed in all three laminopathy models, and in each case, dialing SUN1 back down rescues organismal and/or cellular defects. In *Lmna* mouse models, this is the first example of a genetic intervention that enhances survival, making SUN1 a prime target in the pursuit of therapies.

A number of questions remain. How do SUN1 levels become elevated in laminopathies, and what happens during normal aging? What is the mechanism by which SUN1 overexpression leads to pathologies, in particular, distinct phenotypes in the two *LMNA* models? Remember that loss of A-type lamin function in mouse and humans causes cardiac and skeletal muscle phenotypes, whereas dominant gain-of-function *LMNA* mutations are thought to confer progeria. One possibility is that these genetic interpretations are too simplistic. Progerin localizes to the nuclear periphery and, in a heterozygous state, brings normal lamin A with it (Delbarre et al., 2006). This would be predicted to result in enhanced A-type lamin function at the periphery and reduced function in the interior. In this case, the consequences of progerin expression should partially overlap with that of complete loss of A-type lamins in the knockout but should also have distinct features. Thus, progeroid phenotypes may be a mixture of gain and loss of A-type lamin function.

Like any important study, this report by Chen et al. describes key new findings and simultaneously raises questions for future study. The answers to those questions may unravel the mechanistic underpinnings of multiple types of laminopathies.

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